THE KINETIC SYSTEM.

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In this paper I formulate a theory which I hope will harmonize a large number of clinical and experimental data, supply an interpretation of certain diseases, and show by what means many diverse causes produce the same end effects.

Even should the theory prove ultimately to be true, it will meantime doubtless be subjected to many alterations. The specialized laboratory worker will at first fail to see the broader clinical view, and the trained clinician may hesitate to accept the laboratory findings. Our viewpoint has been gained from a consideration of both lines of evidence on rather a large scale.

The responsibility for the kinetic theory is assumed by myself, while the responsibility for the experimental data is shared fully by my associates, Dr. J. B. Austin, Dr. F. W. Hitchings, Dr. H. G. Sloan and Dr. M. L. Menten.

Introduction.

The self-preservation of man and kindred animals is affected through mechanisms which transform latent energy into kinetic energy to accomplish adaptive ends. Man appropriates from environment the energy he requires in the form of crude food which is refined by the digestive system; oxygen is taken to the blood and carbon dioxid is taken from the blood by the respiratory system; to and from the myriads of working cells of the body, food and oxygen and waste are carried by the circulatory system; the body is cleared of waste by the urinary system; procreation is accomplished through the genital system; but none of these systems are evolved primarily for the purpose of transforming potential energy into kinetic energy for specific ends. Each system transforms such amounts of potential into kinetic energy as are required to perform its specific work; but no one of them transforms latent into kinetic energy for the

purposes of escaping, of fighting, of pursuing; or for combating infection. The stomach, the kidneys, the lungs, the heart strike no physical blow—their rôle is to do certain work to the end that the blow may be struck by another system evolved for that purpose. I propose to offer evidence that there is in the body a system evolved primarily for the transformation of latent energy into motion and into heat. This system I propose to designate the Kinetic System.

The kinetic system does not directly circulate the blood, nor does it exchange oxygen and carbon dioxid; nor does it perform the functions of digestion, urinary elimination and procreation; but though the kinetic system does not directly perform these functions, it does play indirectly an important rôle in each, just as the kinetic system itself is aided indirectly by the other systems.

The principal organs which comprise the kinetic system are the brain, the thyroid, the suprarenals, the liver and the muscles. The brain is the great central battery which drives the body; the thyroid governs the conditions favoring tissue oxidation; the suprarenals govern immediate oxidation processes; the liver fabricates and stores glycogen; and the muscles are the great converters of latent energy into heat and motion.

Adrenalin alone, thyroid extract alone, brain activity alone, and muscular activity alone are capable of causing the body temperature to rise above the normal. The functional activity of no other gland of the body alone, and the secretion of no other gland alone can cause a comparable rise in body temperature—that is, increased functional activity; and no active principle derived from the kidney, the liver, the stomach, the pancreas, the hypophysis, the parathyroid, the spleen, the intestines, the thymus, the lymphatic glands or the bones can, *per se,* cause a rise in the general body temperature comparable to the rise that may be caused by the activity of the brain or the muscles, or by the injection of adrenalin or thyroid extract. Then, too, when the brain, the thyroid, the suprarenals, the liver or the muscles are eliminated, the power of the body to convert latent into kinetic energy is impaired or lost. I shall offer evidence tending to show that an excess of either internal or external environmental stimuli may modify one or more organs of the kinetic system, and that this modification may cause certain diseases. For example,—

alterations in the efficiency of the cerebral link may yield neurasthenia, mania, dementia; of the thyroid link,—Graves' disease, myxedema; of the suprarenal link,—Addison's disease, cardiovascular disease.

This introduction may serve to give the line of our argument. We shall now consider briefly certain salient facts which relate to the conversion of latent energy into kinetic energy as an adaptive reaction. The amount of experimental data is so large that they will later be published in a monograph.

The amount of latent energy which may be converted into kinetic energy for adaptive ends varies in different species, in individuals of the same species, in the same individual in different seasons; in the life cycle of growth, reproduction and decay; in the waking and sleeping hours; in disease and in activity. We shall here consider briefly the reasons for some of those variations and the mechanism which makes them possible.

Biologic Consideration of the Adaptive Variation in Amounts of Energy Stored in Various Animals.

Energy is appropriated from the physical forces of nature that constitute the environment. This energy is stored in the body in quantities in excess of the needs of the moment. In some animals this excess storage is greater than in other animals. Those animals whose self-preservation is dependent on purely mechanical or chemical means of defense, such animals as crustaceans, porcupines, skunks or cobras, have a relatively small amount of convertible (adaptive) energy stored in their bodies. On the contrary, the more an animal is dependent on its muscular activity for self-preservation the more surplus available (adaptive) energy there is stored in its body. It may be true that all animals have approximately an equal amount per kilo of chemical energy—but certainly they have not an equal amount stored in a form which is available for immediate conversion for adaptive ends.

Adaptive Variation in the Rate of Energy Discharge.

What chance for survival would a skunk have without odor; a cobra without venom; a turtle without carapace; or a porcupine

shorn of its barbs, in an environment of powerful and hostile carnivora? And yet in such a hostile environment many unprotected animals survive by their muscular power of flight alone. It is evident that the provision for the storage of "adaptive" energy is not the only evolved characteristic which relates to the energy of the body. The more the self-preservation of the animal depends on motor activity, the greater is the range of variation in the rate of discharge of energy. The rate of energy discharge is especially high in animals evolved along the line of hunter and hunted, such as the carnivora and the herbivora of the great plains.

Influences That Cause Variation in the Rate of Output of Energy in the Individual.

Not only is there a variation in the rate of output of energy among various species of animals, but one finds also variations in the rate of output of energy among individuals of the same species. If our thesis that men and animals are mechanisms responding to environmental stimuli is correct, and further, if the speed of energy output is due to changes in the activating organs as a result of adaptive stimulation, then we should expect to find physical changes in the activating glands during the cycles of increased activation. What are the facts? We know that most animals have breeding seasons evolved as adaptations to the food supply and weather. Hence there is in most animals a mating season in advance of the season of maximum food supply so that the young may appear at the period when food is most abundant. In the springtime most birds and mammals mate, and in the springtime at least one of the great activating glands is enlarged—the thyroid in animals and in man shows seasonal enlargement. The effect of the increased activity is seen in the song, the courting, the fighting, in the quickened pulse and in a slightly raised temperature. Even more activation than that connected with the season is seen in the physical act of mating—when the thyroid is known to enlarge materially, though this increased thyroid activity, as we shall show later, is probably no greater than the increased activity of other activating glands. In the mating season the kinetic activity is speeded up; in short, there exists a state—a fleeting state—of mild Graves' disease; in the early stages of Graves' disease, before

the destructive phenomena are felt, the kinetic speed is high and life is on a sensuous edge. Not only is there a seasonal rhythm to the rate of flow of energy, but there is a diurnal variation, the ebb is at night, and the full tide in the daytime. This observation is verified by experiments which show that certain organs in the kinetic chain are histologically exhausted, the depleted cells being for the most part restored by sleep.

We have seen that there are variations in speed in different species, and that in the same species speed varies with the season of the year and with the time of day. In addition there are variations also in the rate of discharge of energy in the various cycles of the life of the individual. The young are evolved at high speed for growth, so that as soon as possible they may attain to their own power of self-defense; they must adapt themselves to innumerable bacteria; to food, and to all the elements in their external environment. Against their gross enemies the young are measurably protected by their parents; but the parents—except to a limited extent in the case of man—are unable to assist in the protection of the young against infectious disease.

The cycle of greatest kinetic energy for physiologic ends is the period of reproduction. In the female especially there is a cycle of increased activity just prior to her development into the procreative state. During this time secondary sexual characters are developed—the pelvis expands, the ovaries and the uterus grow rapidly, the mammary glands develop. Again in this period of increasing speed in the expenditure of energy we find the thyroid, the suprarenal and the hypophysis also in rapid growth. Without the normal development of the ovary, the thyroid and the hypophysis, neither the male nor the female can develop the secondary sexual characters, nor do they develop sexual desire nor show seasonal cycles of activity, nor can they procreate. The secondary sexual characters—sexual desire, fertility—may be developed at will—for example, by feeding thyroid products from alien species to the individual deprived of the thyroid.

At the close of the childbearing period there is a permanent diminution of the speed of energy discharge, for energy is no longer needed as it was for the self-preservation of the offspring before

adolescence, and for the propagation of the species during the procreative period. Unless other factors intervene this reduction in speed is progressive until senescent death. The diminished size of the thyroid of the aged bears testimony to the part the activating organs bear in the general decline.

We have now referred to variations in the rate of discharge of energy in different species; in individuals of the same species; in cycles in the same individual—such as the seasons of food supply; the periods of wakefulness and of sleep; the procreative period—and we have spoken of those variations caused artificially by thyroid feeding.

Thus far we have referred to the conversion for adaptive purposes of latent into kinetic energy in muscular and in procreative action. We shall now consider the conversion of latent into kinetic energy in the production of heat,[1] and endeavor to answer the questions which arise at once:—Is there one mechanism for the conversion of latent energy into heat and another mechanism for its conversion into muscular action? What is the adaptive advantage of fever in infection?

The Purpose and the Mechanism of Heat Production in Infections.

Vaughn has shown that the presence in the body of any alien protein causes an increased production of heat, and that there is no difference between the production of fever by foreign protein and by infections. Before the day of the hypodermic needle and of experimental medicine, the foreign proteins found in the body outside the alimentary tract were brought in by invading microörganisms. Such organisms interfered with and destroyed the host. The body, therefore, was forced to evolve a means of protection against these hostile organisms. The increased metabolism and fever in infection might operate as a protection in two ways: the increased fever by interfering with bacterial growth, and the increased metabolism by breaking up the bacteria. Bacteriologists have taught us that bacteria grow best at the normal temperature of the body, hence fever

[1] We use the terms heat and muscular action in the popular sense, though physicists use them to designate one and the same kind of energy.

would interfere with bacterial growth. With each rise of one degree centigrade the chemical activity of the body is increased ten per cent. In acute infections there is aversion to food and frequently there is vomiting. In fever, then, we have a diminished intake of energy, but an increased output of energy—hence the available potential energy in the body is rapidly consumed. This may be an adaptation for the purpose of breaking up the foreign protein molecules composing the bacteria. Thus the body may be purified by a chemical combustion so furious that frequently the host itself is destroyed. The problem of immunity is not considered here.

As to the mechanism which produces fever, we postulate that it is the same mechanism as that which produces muscular activity. Muscular activity is produced by the conversion of latent energy into motion, and fever is produced largely in the muscles by the conversion of latent energy into heat. We should, therefore, find similar changes in the brain, the suprarenals, the thyroid, and the liver, whatever may be the purpose of the conversion of energy—whether for running, for fighting, for the expression of emotion, or for combating infection.

We shall first present experimental and clinical evidence which tends to show what part is played by the brain in the production of both muscular and febrile action, and later we shall discuss the parts played by the suprarenals, the thyroid, and the liver.

Histologic Changes in the Brain-Cells in Relation to the Maintenance of Consciousness and to the Production of the Emotions, Muscular Activity and Fever.

We have studied the brain-cells in human cases of fever, and in animals after prolonged insomnia; after the injection of the toxins of gonococci, of streptococci, of staphylococci, and of colon, tetanus, diphtheria and typhoid bacilli; and after the injection of foreign proteins, of indol and skatol, of leucin and of peptones. We have studied the brains of animals which had been activated in varying degrees up to the point of complete exhaustion by running, by fighting, by rage and fear, by physical injury and by the injection of strychnia. We have studied the brains of salmon at the mouth of the Columbia River and at its headwater; the brains of electric fish,

the storage batteries of which had been partially discharged, and of those the batteries of which had been completely discharged; the brains of woodchucks in hibernation and after fighting; the brains of humans who had died from anemia resulting from hemorrhage, from acidosis, from eclampsia, from cancer, and from other chronic diseases. We have studied also the brains of animals after the excision of the suprarenals, of the pancreas, and of the liver.

In every instance the loss of vitality—that is, the loss of the normal power to convert potential into kinetic energy—was accompanied by physical changes in the brain-cells. The converse was also true—that is, the brain-cells of animals with normal vital power showed no histologic changes. The changes in the brain-cells were identical whatever the cause. The crucial question then becomes: Are these constant changes in the brain-cells the result of work done by the brain-cells in running, in fighting, in emotion, in fever? In other words, does the brain perform a definite rôle in the conversion of latent energy into fever or into muscular action; or are the brain-cell changes caused by the chemical products of metabolism? Happily this crucial question was definitely answered by the following experiment: The circulations of two dogs were crossed in such a manner that the circulation of the head of one dog was anastomosed with the circulation of the body of another dog and vice versa. A cord encircled the neck of each so firmly that the anastomosing circulation was blocked. If the brain-cell changes were due to the metabolic products, then when the body of dog "A" was injured, the brain of dog "A" would be normal and the brain of dog "B" would show changes. Our experiments showed brain-cell changes in the brain of the dog injured and no changes in the brain of the uninjured dog.

The injection of adrenalin causes striking brain-cell changes—first, a hyperchromatism, then a chromatolysis. Now if adrenalin caused these changes merely as a metabolic phenomenon and not as a "work" phenomenon, then the injection of adrenalin into the carotid artery of a crossed circulation dog would cause no change in its circulation and its respiration, since the brain thus injected is in exclusive vascular connection with the body of another dog. In our experiment the blood-pressures of both dogs were recorded on a drum when adrenalin was injected into the common carotid. The adre-

nalin caused a rise in blood-pressure, an increase in the force of cardiac contraction, increase in respiration, and a characteristic adrenalin rise in the blood-pressure of both dogs. The rise was seen first in the dog whose brain alone received adrenalin and about a minute later in the dog whose body alone received adrenalin. Histologic examinations of the brains of both dogs showed marked hyperchromatism in the brain receiving adrenalin, while the brain receiving no adrenalin showed no change. Here is a clear-cut observation on the action of adrenalin on the brain—and both the functional and the histological tests showed that adrenalin causes increased brain action. The significance of this affinity of the brain for adrenalin begins to be seen when I call attention to the following striking facts:

1. Adrenalin alone causes hyperchromatism followed by chromatolysis, and in overdosage causes the destruction of some brain-cells.

2. When the suprarenal glands are both excised and no other factor is introduced, the Nissl substance progressively disappears from the brain-cells until death. This far-reaching point will be taken up later.

Here our purpose is to discuss the cause of the brain-cell changes. We have seen that in crossed brain and body circulation trauma cause changes in the cells of the brain which is disconnected from the traumatized body by its circulation, but which is connected with the traumatized body by the nervous system. We have seen that adrenalin causes activation of the body connected with its brain by the nervous system, and histologic changes in the brain acted on directly by the adrenalin, but we found no brain-cell changes in the other brain through which the products of metabolism have circulated.

In the foregoing we find direct evidence that the brain-cell changes are not due to the products of metabolism. We shall now present evidence to show that the brain-cell changes are "work" changes. What work? We postulate that it is the work by which the energy stored in the brain-cells is converted into electricity or some other form of transmissible energy which then activates certain glands and muscles, thus converting latent energy into heat and motion. It has chanced that certain other studies have given an analogous and convincing proof of this postulate. In the electric fish a part of the muscular mechanism is replaced by a specialized structure for storing

and discharging electricity. We found "work" changes in the brain-cells of electric fish after all their electricity had been rapidly discharged. We found further that electric fish could not discharge their electricity when under anesthesia, and clinically we know that under deep morphia narcosis, and under anesthesia, the production both of heat and of muscular action is hindered. The action of morphia in lessening fever production is probably the result of its depressing influence on the brain-cells, because of which a diminished amount of their potential energy is converted into electricity and a diminished electric discharge from the brain to the muscles should diminish heat production proportionally. We found by experiment that under deep morphinization brain-cell changes due to toxins could be largely prevented; in human patients deep morphinization diminishes the production of muscular action and of fever, and as we shall see later conserves life when it is threatened by acute infections. The contribution of the brain-cells to the production of heat is either the result of the direct conversion of their stored energy into heat, or of the conversion of their latent energy into electricity or a similar force, which in turn causes certain glands and muscles to convert latent energy into heat.

A further support to the postulate that the brain-cells contribute to the production of fever by sending impulses to the muscles is found in the effect of muscular exertion, or of other forms of motor stimulation in the presence of a fever-producing infection. Under such circumstances muscular exertion causes additional fever, and causes also added but identical changes in the brain-cells. Thyroid extract and iodin have the same effect as muscular exertion and infection in the production of fever and the production of brain-cell changes. All of this evidence is a strong argument in favor of the theory that certain constituents of the brain-cells are consumed in the work performed by the brain in the production of fever.

That the stimulation of the brain-cells without gross activity of the skeletal muscles and without infection can produce heat is shown as follows:

(*a*) Fever is produced when animals are subjected to fear without any consequent exertion of the skeletal muscles.

(*b*) The temperature of the anxious friends of patients will rise while they await the outcome of an operation.

(*c*) The temperature of patients will rise as a result of the mere anticipation of a surgical operation.

(*d*) There are innumerable clinical observations as to the effect of emotional excitation on the temperature of patients. A rise of a degree or more is a common result of a visit from a tactless friend. There is a traditional Sunday increase of temperature in hospital wards. Now the visitor does not bring and administer more infection to the patient to cause this rise, and the rise of temperature occurs even if the patient does not make the least muscular exertion as a result of the visit. I observed an average increase of one and one eighth degrees of temperature in a ward of fifteen children as a result of a Fourth of July celebration.

Is the contribution of the brain to the production of heat due to the conversion of latent energy directly into heat, or does the brain produce heat principally by converting its latent energy into electricity or some similar form of transmissible energy which through nerve connections stimulates other organs and tissues, which in turn convert their stores of latent energy into heat?

According to Starling, when the connection between the brain and the muscles of an animal is severed by curare, by anesthetics, by the division of the cord and nerves, then the heat-producing power of the animal so modified is on a level with that of cold-blooded animals. With cold the temperature falls, with heat it rises. Such an animal has no more control over the conversion of latent energy into heat than it has over the conversion of latent energy into motion.

Electric stimulation done over a period of time causes brain-cell changes, and electric stimulation of muscles causes a rise in temperature.

Summary.

In our crossed circulation experiments we found that the brain-cell changes were not due to waste products or to metabolic poisons. We found that in the production both of muscular action and of fever there were brain-cell changes which showed a quantitative relation to the temperature changes or to the muscular

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work done. We observed that under deep morphinization the febrile response or the muscular work done was either diminished or eliminated and that the brain-cell changes were correspondingly diminished or eliminated. We found also that brain-cell changes and muscular work followed electric stimulation alone. I conclude, therefore, that the brain-cell changes are work changes.

We shall next consider other organs of the kinetic system in their relation to muscular activity, to emotion, to consciousness, to sleep, to hibernation, and to heat production.

The Suprarenal Gland.

In our extensive study of the brain in its relation to the production of energy and consequent exhaustion caused by fear and rage; by the injection of foreign proteins, of bacterial toxins and of strychnin; by anaphylaxis; by the injection of thyroid extract, of adrenalin, and of morphin; we found that with the exception of morphin each of these agents produced identical changes in the brain-cells. As we believed that the suprarenal glands were intimately associated with the brain in its activities, we concluded that the suprarenals also must have been affected by each of these agents. To prove this relation, we administered the above-mentioned stimuli to animals and studied their effects upon the suprarenal glands by functional, histological and surgical methods, the functional tests being made by Cannon's method.

Functional Study of the Suprarenal Glands by Cannon's Method.

Our method of applying the Cannon test for adrenalin was as follows: (*a*) The blood of the animal's was tested before the application of the stimulus. If this test was negative, then (*b*) the stimulus was applied and the blood again tested. If this test was negative, a small amount of adrenalin was added. If a positive reaction was then given, the negative result was accepted as conclusive. (*c*) If the control test was negative, then the stimulus was given. If the blood after stimulation gave a positive result for adrenalin, a second test of the same animal's blood was made twenty-five minutes or

more later. If the second test was negative, then the positive result of the first test was accepted as conclusive.

We have recorded sixty-six clear-cut experiments on dogs, which show that after fear and rage, after anaphylaxis, after injections of indol and skatol, of leucin and tyrosin, of the toxins of diphtheria and colon bacilli, of streptococci, and staphylococci, of foreign proteins and of strychnin, the Cannon test for adrenalin was positive. The test was negative after trauma under anesthesia, and after intravenous injections of thyroid extract, of thyroglobin and of the juices of various organs injected into the same animal from which the organs were taken. Placental extract gave a positive test. The test was sometimes positive after electric stimulation of the splanchnic nerves. On the other hand, if the nerve supply to the suprarenals had been previously divided, or if the suprarenals had been previously excised, then the Cannon test was negative, after the administration of each of the foregoing adequate stimuli. Blood taken directly from the suprarenal vein gave a positive result, but under deep morphinization the blood from the suprarenal vein was negative, and under deep morphinization the foregoing adequate stimuli were negative.

In brief, the agencies that in our brain-cell studies were found to cause hyperchromatism followed by chromatolysis, gave positive results in the Cannon test for adrenalin. The one agent which was found to protect the brain against changes in the Nissl substance—morphin—gave a negative result in the Cannon test for adrenalin. After excision of the suprarenals, or after division of their nerve supply, all Cannon tests for adrenalin were negative.

Histologic Studies of the Suprarenal Glands.

Histologic studies of the suprarenal glands after the application of the adequate stimuli which gave positive results to the Cannon tests for adrenalin are now in progress and thus far the histologic studies corroborate the functional tests.

In hibernating woodchucks, the cells of the adrenal cortex were found to be vacuolated, and shrunken. In 100 hours of insomnia, in surgical shock, in strong fear, in exhaustion from fighting, in peptone injections, in acute infections, the suprarenal glands undergo

histological changes characteristic of exhaustion. Alkalies cause suprarenal changes, but acids do not.

We have shown that brain and suprarenal activity go hand in hand—that is, that the suprarenal secretion activates the brain, and that the brain activates the suprarenals. The fundamental question which now arises is this: Are the brain and the suprarenals interdependent? A positive answer may be given to this question, for the evidence of the dependence of the brain upon the suprarenals is as clear as is the evidence of the dependence of the suprarenals upon the brain. (1) After excision of the suprarenals, the brain-cells undergo continuous histological and functional deterioration until death. During this time the brain progressively loses its power to respond to stimuli and there is also a progressive loss of muscular power and a diminution of body temperature. (2) In our crossed circulation experiments we found that adrenalin alone could cause increased brain activity, while histologically we know that adrenalin alone causes an increase of the Nissl substance. An animal both of whose suprarenals had been excised showed no hyperchromatism in the brain-cells after the injection of strychnin, of toxins, of foreign proteins, etc. (3) When the suprarenal nerve supply was divided (Cannon-Elliott), then there was no increased suprarenal activity in response to adequate stimuli.

From these studies we are forced to conclude not only that the brain and suprarenals are interdependent, but that the brain is actually more dependent upon the suprarenals than the suprarenals upon the brain, since the brain deteriorates progressively to death without the suprarenals, while the suprarenals whose connection with the brain has been broken by the division of their nerve supply will still produce sufficient adrenalin to support life.

From the strong affinity of the brain-cells for adrenalin which was manifested in our experiments, we may strongly suspect that the Nissl substance is a volatile, extremely unstable combination of certain elements of the brain-cells and adrenalin because the suprarenal glands alone do not take the Nissl stain and the brain deprived of adrenalin does not take Nissl stain. The consumption of the Nissl substance in the brain-cells is lessened or prevented by morphin as is the output of adrenalin; and the consumption of the Nissl substance

is also lessened or prevented by nitrous oxid. But morphin does not prevent the action of adrenalin injected into the circulation, hence the control of morphin over energy expenditure is exerted directly on the brain-cells. Apparently morphin and nitrous oxid both act through this interference with oxidation in the brain. We, therefore, conclude that within a certain range of acidity of the blood adrenalin can unite with the brain-cells only through the mediation of oxygen, and that the combination of adrenalin, oxygen, and certain brain-cell constituents causes the electric discharge that produces heat and motion. In this interrelation of the brain and the suprarenals, we have what is perhaps the master key to the automatic action of the body. Through the special senses environmental stimuli reach the brain and cause it to liberate energy which in turn activates certain other organs and tissues, among which are the suprarenal glands. The increased output of adrenalin activates the brain to still greater activity, as a result of which again the entire sympathetic nervous system is further activated, as is manifested by increased heart action, more rapid respiration, raised blood-pressure, increased output of glycogen, increased power of the muscles to metabolize glucose, etc.

If this conclusion is well founded, we should find corroborative evidence in histologic changes in that great store-house of potential energy, the liver, as a result of the application of each of the adequate stimuli which produced brain-cell and suprarenal changes.

The Liver.

Prolonged insomnia, prolonged physical exertion, infections, injections of toxins, and of strychnin, rage and fear, physical injury under anesthesia, in fact all of the adequate stimuli which affected the brain and the suprarenals, produced constant and identical histologic changes in the liver—the cells stained poorly, the cytoplasm was vacuolated, the nuclei were crenated, the cell membranes were irregular, the most marked changes occurring in the cells of the periphery of the lobules. In prolonged insomnia the striking changes in the liver were repaired by one seance of sleep.

Are the histologic changes in the liver cells due to metabolism or toxic products or are they "work" changes incident to the conversion of latent into kinetic energy? Are the brain, suprarenals and liver

interdependent? The following facts establish the answers to these queries:

1. The duration of life after excision of the liver is about the same as after adrenalectomy—approximately eighteen hours.

2. The amount of glycogen in the liver was diminished in all of the experiments showing brain-suprarenal activity; and when the histologic changes were repaired, the normal amount of glycogen was again found.

3. In crossed circulation experiments changes were found in the liver of the animal whose brain received the stimulus.

From these premises we must consider that the brain, the suprarenals, and the liver are mutually dependent on each other for the conversion of latent into kinetic energy. Each is a vital organ—each equally vital. It may be said that excision of the brain may apparently cause death in less time than excision of the liver or suprarenals, but this statement must be modified by our definition of death. If all the brain of an animal be removed by decapitation, its body may live on for at least eleven hours if its circulation be maintained by transfusion. An animal may live for weeks or months after excision of the cerebral hemispheres and the cerebellum, while an overtransfused animal may live many hours, for days, even after the destruction of the medulla. It is possible even that the brain actually is a less vital organ than either the suprarenals or the liver.

In our research to discover whether any other organs should be included with the brain, the suprarenals and the liver in this mutually interdependent relation, we hit upon an experiment which throws light upon this problem.

Groups of rabbits were gently kept awake for 100 hours by relays of students,—an experiment which steadily withdrew energy but caused not the slightest physical or emotional injury to any of them; no drug, toxin, or other agent was given to them; they were given sufficient food and drink. In brief, the internal and external environments of these animals were kept otherwise normal excepting for the gentle stimuli which ensured continued wakefulness. This protracted insomnia gradually exhausted the animals completely, some to the point of death even. Some of the survivors were killed im-

mediately after the expiration of 100 hours of wakefulness, others after varying intervals.

Histological studies were made of every tissue and organ in the body. Three organs, the brain, the suprarenals, and the liver, and these three only showed histologic changes. In these three organs the histologic changes were marked, and were almost wholly repaired by one seance of sleep. In each instance these histologic changes were identical with those seen after physical exertion, emotions, toxins, etc. It would appear, then, that these three organs take the stress of life—the brain is the battery, the suprarenals the oxidizer, and the liver the gasoline tank. The clear-cut insomnia experiment corresponds precisely with our other brain-suprarenal observations.

With these three kinetic organs we may surely associate also the "furnace," the muscles in which the energy provided by the brain, suprarenals and liver, plus oxygen, is fabricated into heat and motion.

Benedict in his monumental work on metabolism has demonstrated that in the normal state, at least, variations in the heart beat parallel variations in metabolism. He and others have shown that all energy of the body, whether evidenced by heat or by motion, is produced in the muscles. In the muscles then, we find the fourth vital link in the kinetic chain. The muscles move the body, circulate the blood, effect respiration, and govern the body temperature. They are the passive servants of the brain-suprarenal-liver syndrome.

Neither the brain, the suprarenals, the liver, nor the muscles, however, nor all of these together, have the power to change the rate of the expenditure of energy; to make possible the increased expenditure in adolescence, in pregnancy, in courting and mating, in infections. No one of these organs, nor all of them together, can act as a pacemaker or sensitizer. The brain acts immediately in response to the stimuli of the moment; the suprarenals respond instantly to the fickle brain and the effects of their actions are fleeting; the liver contains fuel only and cannot activate, and the muscles in turn act as the great furnace, in which the final transformation into available energy is made.

Another organ—the thyroid—has the special power of governing the *rate* of *discharge* of energy; in other words, the thyroid is the pace-maker. Unfortunately, the thyroid cannot be studied to

advantage either functionally or histologically, for there is as yet no available test for thyroidism in the blood as there is for adrenalin, and thyroid activity is not attended by striking histologic changes. Therefore the only laboratory studies which have been satisfactory thus far are those by which the iodin content of the thyroid has been established. Iodin is stored in the colloid lacunæ of the thyroid and in combination with certain proteins is the active agent of the thyroid.

Beebe has shown that electrical stimulation of the nerve supply of the thyroid diminishes the amount of iodin which it contains and it is known that in the hyperactive thyroid in Graves' disease the iodin content is diminished. The meagerness of laboratory studies, however, is amply compensated by the observations which the surgeon has been able to make on a vast scale—observations which are as definite as are the results of laboratory experiments.

The Thyroid.

The brain-cells and the suprarenal glands are securely concealed from the eye of the clinician, hence the changes produced in them by different causes escape his notice, but the thyroid has always been closely scrutinized by him. The clinician knows that every one of the above mentioned causes of increased brain-cell, suprarenal, liver and muscle activity may cause an increase in the activity of both the normal or the enlarged thyroid; and he knows only too well that in a given case of exophthalmic goiter, the same stimuli which excite the brain, the suprarenals, the liver, and the muscles to increased activity will also aggravate this disease.

The function of the thyroid in the kinetic chain is best evidenced, however, by its rôle in the production of fever. Fever results from the administration of thyroid extract alone in large doses. In the hyper-activity of the thyroid in exophthalmic goiter, one sees a marked tendency to fever; in severe cases there is daily fever. In fact, in Graves' disease we find displayed to an extraordinary degree an exaggeration of the whole action of the kinetic mechanism.

We have stated that in acute Graves' disease there is a tendency to the production of spontaneous fever, and that there is a magnified diurnal variation in temperature which is due to an increased output of energy in even the normal reaction producing consciousness. In

Graves' disease there is, therefore, a state of intensified consciousness, which is associated with low brain thresholds to all stimuli—both to stimuli that cause muscular action and to stimuli that cause fever. The intensity of the kinetic discharge is seen in the constant fine tremor. It is evident that the thresholds of the brain have been sensitized. In this hypersensitization we find the following strong evidence as to the identity of the various mechanisms for the production of fever. In the state of superlative sensitization which is seen in Graves' disease, we find that the stimuli that produce muscular movement, the stimuli that produce emotional phenomena and the stimuli that produce fever are as nearly as can be ascertained equally effective. Clinical evidence regarding this point is abundant, for in patients with Graves' disease we find that the three types of conversion of energy resulting from emotional stimulation, from nociceptor stimulation (pain), and from infection stimulation are, as nearly as can be judged, equally exaggerated. In the acute cases of Graves' disease the explosive conversion of latent energy into heat and motion is unexcelled by any other known normal or pathological phenomenon. Excessive thyroid secretion, as in thyrotoxicosis from functioning adenomata, and excessive thyroid feeding, cause all the phenomena of Graves' disease except the exophthalmos and the emotional facies. Ligation of arteries, division of nerve supply and excision of part of the gland may reverse the foregoing picture and restore the normal condition. The patient notes the effect on the second day and often within a week is relatively quiescent. On the contrary if there is thyroid deficiency there is the opposite state, a reptilian sluggishness.

At will, then, through diminished, normal or excessive administration of thyroid secretion, we may produce an adynamic, a normal, or an excessively dynamic state. By the thyroid influence, the brain thresholds are lowered and life becomes exquisite; without its influence the brain becomes a globe of relatively inert substance. Excessive doses of iodin alone cause most of the symptoms of Graves' disease. The active constituent of the thyroid is iodin in a special protein combination. Thus is stored in the colloidal spaces. Hence one would not expect to find changes in the cells of the thyroid gland as a result of increased activity unless it be prolonged.

We have thus far considered the normal rôles played by the brain, the suprarenals, the liver, the muscles and the thyroid in transforming latent into kinetic energy in the form of heat and motion as an adaptive response to environmental stimuli.

The argument may be strengthened, however, by the discussion of the effect of the impairment of any of these links in the kinetic chain upon the conversion of latent into kinetic energy.

Effect Upon the Output of Energy of Impaired or Lost Function of Each of the Several Links in the Kinetic Chain.

1. *The Brain: Cerebral softening.*—In cerebral softening we may find all the organs of the body comparatively healthy excepting the brain. As the brain is physically impaired it cannot normally stimulate other organs to the conversion of latent energy into heat or into motion, but on the contrary in these cases we find feeble muscular and intellectual power. I believe also we find that in patients with cerebral softening, infections such as pneumonia show a lower temperature range than in patients whose brains are normal.

2. *The Suprarenals.*—In such destructive lesions of the suprarenal glands as Addison's disease one of the cardinal symptoms is a subnormal temperature and impaired muscular power. Animals upon whom double adrenalectomy has been performed show a striking fall in temperature, muscular weakness—after adrenalectomy the animal may not be able to stand even—and progressive chromatolysis. The significance of the last will be pointed out later.

3. *The Liver.*—When the function of the liver is impaired by tumors, cirrhosis, or degeneration of the liver itself, then the entire energy of the body is correspondingly diminished. This diminution of energy is evidenced by muscular and mental weakness, by diminished response and by a gradual loss of efficiency which finally reaches the state of asthenia.

4. *The Muscles.*—It has been observed clinically that if the muscles are impaired by long disuse, or by a disease such as myasthenia gravis, then the range of production of both heat and motion is below normal. This is in agreement with the experimental findings that anesthetics, curare, or any break in the muscle-brain connection causes diminished muscular and heat production.

5. *The Thyroid.*—In myxedema one of the cardinal symptoms is a persistently subnormal temperature and though prone to infection, subjects of myxedema show but feeble febrile response and readily succumb. This clinical observation is strikingly confirmed by laboratory observations; normal rabbits subjected to fear showed a rise in temperature of from one to three degrees while two rabbits whose thyroids had been previously removed and who had then been subjected to fright showed much less febrile response. Myxedema subjects show a loss of physical and mental energy which is proportional to the lack of thyroid. Deficiency in any of the organs of the kinetic chain causes alike loss of heat, loss of muscular and emotional action, of mental power and of the power of combating infections—the negative evidence thus strongly supports the positive. By accumulating all the evidence we believe we are justified in associating the brain, the suprarenals, the thyroid, the muscles and the liver as vital links in the kinetic chain. Other organs play a rôle undoubtedly, though a minor one. If our conclusions are sound, then in the kinetic system we should find an explanation of many diseases, and having found an explanation, we may find new methods of combating them.

Kinetic Diseases.

In the foregoing conclusions we find a simple explanation of certain diseases. When the kinetic system is driven at an overwhelming rate of speed—as by severe physical injury, by intense emotional excitation, by perforation of the intestines, by the pointing of an abcess into new territory, by the sudden onset of an infectious disease, by an overdose of strychnin, by a Marathon race, by a grilling fight, by foreign proteins, by anaphylaxis,—the result of these acute overwhelming activations of the kinetic system is clinically designated shock, and according to the cause is called traumatic shock, toxic shock, anaphylactic shock, drug shock, etc.

The essential pathology of shock is identical whatever the cause. If, however, instead of an intense overwhelming activation, the kinetic system is continuously or intermittently overstimulated through a considerable period of time, as long as each of the links in the kinetic chain takes the strain equally the result will be excessive

energy conversion, excessive work done; but usually, under stress, some one link in the chain is unable to take the strain and then the evenly balanced work of the several organs of the kinetic system is disturbed. If the brain cannot endure this strain, then neurasthenia, nerve exhaustion, or even insanity follows. If the thyroid cannot endure the strain it undergoes hyperplasia, which in turn may result in a colloid goiter or in exophthalmic goiter. If the suprarenals cannot endure the strain, cardiovascular disease may develop. If the liver cannot take the strain then death from acute acidosis may follow, or if the neutralizing effect of the liver is only partially lost, then the acidity may cause Bright's disease. Over-activation of the kinetic system may cause glycosuria and diabetes.

Identical physical and functional changes in the organs of the kinetic system may result from intense continued stimulation from any of the following causes, excessive physical labor, athletic exercise, worry or anxiety, intestinal auto-intoxication, chronic infections such as oral sepsis, tonsillitis and adenoids; chronic appendicitis, chronic cholecystitis, colitis, and skin infections; the excessive intake of protein food (foreign protein reaction); emotional strain, pregnancy, stress of business of professional life—all of which are known to be activators of the kinetic system.

From the foregoing statements we are able to understand the muscular weakness following fever; we can understand why the senile have neither muscular power nor strong febrile reaction; why long-continued infections produce pathologic changes in the organs constituting the kinetic chain; why the same pathologic changes result from various forms of activation of the kinetic system. In this hypothesis we find a reason why cardiovascular disease may be caused by chronic infection, by auto-intoxication, by overwork, or by emotional excitation. We now see that the reason why we find so much difficulty in differentiating the numerous acute infections from each other is because they play upon the same kinetic chain. Our postulate harmonizes the pathological democracy of the kinetic organs, for it explains not only why in many diseases the pathological changes in these organs are identical, but why the same changes are seen as the result of emotional strain and overwork. We can

thus understand how either emotional strain or acute or chronic infection may cause either exophthalmic goiter or cardiovascular disease; how chronic intestinal stasis with the resultant absorption of toxins may cause cardiovascular disease; neurasthenia or goiter. Here is found an explanation of the phenomena of shock, whether the shock be the result of toxins, of infection, of foreign proteins, of anaphylaxis, of psychic stimuli, or of a surgical operation with its combination of both psychical and traumatic elements.

This conception of the kinetic system has stood a crucial test by making possible the shockless surgical operation. It has offered a plausible explanation of the cause and the treatment of Graves' disease. Will this kinetic theory stand also the clinical test of controlling that protean disease bred in the midst of the stress of our present-day life? Present-day life, in which one must ever have one hand on the sword and the other on the throttle, is a constant stimulus of the kinetic system. The force of these kinetic stimuli may be lessened at the cerebral link by intelligent control—a protective control is empirically attained by many of the most successful men. The force of the kinetic stimuli may be broken at the thyroid link by dividing the nerve supply, reducing the blood supply, or by partial excision; or if the suprarenals feel the strain, the stimulating force may be broken by dividing their nerve supply, reducing the blood supply, or by partial excision. No theory is worth more than its yield in practice, but already we have the shockless operation, the surgical treatment of Graves' disease, the control of shock and the acute infection by overwhelming morphinization.

Conclusions.

To become adapted to their environment animals are transformers of energy. This adaptation to environment is made by means of a system of organs evolved for the purpose of converting potential energy into heat and motion. The principal organs and tissues of this system are the brain, the suprarenals, the thyroid, the muscles and the liver. Each is a vital link—each plays its particular rôle and one cannot compensate for the other. A change in any link

of the kinetic chain modifies proportionately the entire kinetic system, which is no stronger than its weakest link.

In this conception we find a possible explanation of many diseases —one which may point the way to new and more effective therapeutic measures than those now at our command.

CLEVELAND, O.,
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